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July 17, 2000

Dockets Management Branch (HFA-305)
Food and Drug Administration
5630 Fishers Lane, Room 1061
Rockville, MD 20852

Re: Response to Docket No. 97N-0497, "Request for proposed standards for unrelated allogeneic peripheral and placental/umbilical cord blood hematopoietic stem/progenitor cell products" (Federal Register April 18, 2000; volume 65 [75]: 20825).

To Whom It May Concern:

This letter is in response to the above-named docket as it pertains specifically to the use of unrelated donor umbilical cord blood (UCB). In our attempt to assist in the development of specific product standards for unrelated donor UCB, we provide compiled data from our on-going analysis of clinical results of UCB transplantation. This summary has been generated from the combined data sets of consecutively transplanted patients from Duke University and the University of Minnesota, the two clinical transplant programs with the largest series on UCB transplantation in the United States. We present a summary rather than individual patient data to protect patient confidentiality and to preserve our ability to publish this data in the medical literature. We will, however, permit the FDA to review this data in a confidential setting if this is requested as the review of the docket proceeds over the next year.

Introduction

Transplantation of hematopoietic stem cells (HSC) derived from bone marrow and UCB of HLA-identical sibling donors has been successfully utilized in the treatment of patients with high-risk or recurrent hematological malignancies, bone marrow failure syndromes, selected hereditary immunodeficiency states and metabolic disorders. Successful use of HSC transplant therapy, however, has been limited by a lack of HLA matched donors and the high risk of graft-versus-host disease (GVHD) after transplantation. While there are currently 4-5 million HLA-A, B and DR typed marrow donors registered in marrow donor registries around the world, more than 30% of patients requiring transplant therapy are still unable to find an HLA 0-1 allele disparate living adult marrow donor, with even greater proportions of unsuccessful searches in patients of non-Northern European descent. For those transplanted with unrelated donor marrow, increased HLA disparity has clearly been shown to adversely affect survival. Severe acute and extensive chronic GVHD and increased risk of opportunistic infection limit the successful use of unrelated donor bone marrow transplantation (BMT). While T-cell depletion of unrelated bone marrow has decreased the incidence of acute GvHD, this benefit has been offset by an increased incidence of death from graft failure and relapse in selected diseases. Thus, the rationale for evaluating an alternative stem cell source remains.

Over the past decade, to potentially alleviate the shortage of suitable donors and reduce the length of the marrow donor search process, public, unrelated, placental/UCB banks were created.

with the support of the National Institutes of Health or private corporations. To date approximately 25,000 cord blood units (CBUs) have been banked for public use worldwide. While an estimated 1500 UCB transplants have been performed to date, few have been reported. Gluckman et al. and Rubinstein et al have reported overlapping registry data.

Since the publication of the two preliminary reports in 1996 (Kurtzberg et al., New Engl J Med; Wagner et al., Blood), nearly 375 unrelated donor UCB transplant have been performed at Duke University and University of Minnesota. In July 2000, a detailed analysis of the combined data sets to determine the potential influence of various factors (e.g., graft cell dose and donor/recipient HLA disparity) on rate of hematopoietic recovery and probabilities of engraftment, acute GVHD, chronic GVHD, non relapse mortality, leukemic relapse and overall survival was initiated. Preliminary results of this analysis are summarized in this letter. Once completed, the entire data analysis will be made available to the Food and Drug Administration.

Patients and methods

As previously presented, patients with acute leukemia, bone marrow failure syndromes, immunodeficiency states or inborn errors of metabolism were eligible for unrelated donor UCB transplantation if: 1) an HLA-compatible related or unrelated bone marrow donor was not available at the time needed, and 2) the subject/parent(s) consented to the transplant procedure. At the University of Minnesota, patients were preferentially offered BMT before UCB transplantation. The majority of patients referred to Duke University had already failed to identify a suitable bone marrow donor for their transplant. Protocols for myeloablative therapy and use of unrelated donor UCB for transplantation were reviewed and approved by the respective institutional review boards at Duke University Medical Center and the University of Minnesota.

Patients

Between August 1993 and April 15, 2000, 312 consecutive patients were transplanted with unmanipulated, banked unrelated donor UCB at Duke University and the University of Minnesota (excluding initial transplants as part of the COBLT study). UCB units were primarily obtained from the Placental Blood Program of the New York Blood Center and St. Louis Cord Blood Bank. For this analysis, patients transplanted with <100 days follow-up or those patients transplanted with ex vivo expanded cells (n=27), had history of prior allogeneic HSC transplantation (n=24), an HLA 4 antigen mismatched UCB donor (n=2), or had less than a conventional myeloablative therapy (n=2) were excluded. Therefore, 257 patients treated for various malignant and non-malignant disorders were evaluable. Patient demographic and treatment characteristics are shown in Table 1. Median age of the patients was 8.1 years (range, 0.2-58) and median weight was 24.5 kg (range, 3.9-102.8).

HLA typing and unrelated donor selection

All unrelated donor UCB units were HLA typed at the UCB bank. Prior to transplantation, confirmatory HLA typing of the selected UCB unit and recipient was preformed at the transplant center and/or the UCB bank. HLA-A and HLA-B antigens were typed using the standard two-stage complement-dependent microcytotoxicity assay, and antigens were assigned as defined at the serologic level by the World Health Organization (WHO) HLA nomenclature committee. HLA-DRB1 type was determined by hybridization of polymerase chain reaction (PCR) amplified DNA with sequence-specific oligonucleotide probes (SSOP) or by DNA sequencing if needed.

HLA-matching was scored at the serologic level for HLA-Class I A and B antigens and at the DNA level for DRB1alleles. Matching at HLA-C or other DR, DP, or DQ antigens or alleles was

not scored. The methods of donor graft selection varied over time. Initially, a graft that most closely HLA matched the recipient was selected; if more than one graft existed at that level of HLA disparity, the graft with the highest cell dose was chosen. More recently, within the confines of ≤2 HLA antigen disparities, the donor graft with the greatest nucleated cell dose was prioritized. The patients transplanted at Duke University received more disparate grafts than the patients transplanted at the University of Minnesota.

Preparative regimen and GVHD prophylaxis

Pretransplant conditioning varied according to the patient's disease, disease status and transplant institution. At the University of Minnesota, 94% patients received a total body irradiation (TBI)-containing regimen and at Duke University, 56% patients received TBI. Preparative regiments for patients with malignant conditions utilized melphalan at Duke and cyclophosphamide at the University of Minnesota. Some patients with non-malignant conditions received chemotherapy with busulfan + cyclophosphamide. Most patients received anti-thymocyte globulin (ATG) prior to unrelated donor UCB transplantation. Prophylaxis for acute GVHD primarily consisted of cyclosporine A (CsA) or CsA and methylprednisolone (MP). At the University of Minnesota, all patients received MP 1 mg/kg every 12 hours on days 5-19 with a 25% taper every other day thereafter (discontinued by day 26 after transplantation). At Duke University, patients received either high dose MP (N = 69) 10 mg/kg on days 5-7, 5 mg/kg on days 8-10, 3 mg/kg on days 11-13 and 2 mg/kg on days 14-17 with a 10% taper per week thereafter (discontinued by 13 weeks after transplantation) or lower dose MP 1 mg/kg on days 0-4 and 2 mg/kg on days 5-19 with a 10% taper per week thereafter. CsA was continued at least 6 months (Minnesota) or 9 months (Duke) before initiating a 10% per week taper.

Transplantation of UCB

Characteristics of the UCB grafts used for transplantation in this study are shown in Table 2. The method of UCB collection has been previously reported by the various banks. Cryopreserved units of UCB were transported to the transplant center via overnight delivery in a dry shipper previously cooled by liquid nitrogen (temperature <-150°C) before the initiation of the preparative regimen and then maintained in the vapor phase of liquid nitrogen at the transplant center until the day of transplantation. With few exceptions, the unit was thawed in the marrow processing laboratory in a 37°C water bath with gentle agitation, using the method described by Rubinstein et al (PNAS, 1995). After rapid thawing in a 37°C waterbath, an equal volume of dextran/albumin solution was added over 5-10 minutes, centrifuged at 400 g for 5-10 minutes at 4°C and the supernatant removed. The cell pellet was resuspended in 30-100 ml of dextran/albumin and infused into the patient over 10-30 minutes to 4 hours.

Supportive care

All patients at Duke University and a majority (66%) of patients at the University of Minnesota received granulocyte-colony stimulating factor (G-CSF, 5-10 ug/kg/day) from day 0. Other aspects of supportive care have been previously published. Briefly, all patients were hospitalized in single rooms under HEPA filtration and supported with parenteral fluids and nutrition, irradiated, leukocyte-depleted PRBC and platelet transfusions, low dose heparin for prophylaxis of veno-occlusive disease (VOD), antifungal and antiviral prophylaxis, emperic parenteral antibiotics for fever, mouth and skin care. At Duke University, patients with a history of or active invasive fungal disease were supported with daily transfusions of G-CSF-mobilized, irradiated granulocytes during their aplasia.

Hematopoietic recovery and engraftment

Hematologic recovery was defined as time to absolute neutrophil count (ANC) $\geq 5 \times 10^8$/L (first of three consecutive laboratory measurements on different days) and platelet count $\geq 5 \times 10^{10}$/L (first of seven consecutive laboratory measurements on different days without transfusion support). Donor cell engraftment and remission status in the marrow were assessed on days 21-42, 100, 6 months, 1 year and 2 years after transplantation with chimerism status determined by molecular polymorphic markers. Complete chimerism was defined as the presence of donor hematopoietic cells only; mixed chimerism was defined as the presence of both donor and host hematopoietic cells (>10%) simultaneously; and, autologous recovery was defined as the presence of host hematopoietic cells (>90%).

Graft-versus-host disease

Patients were evaluated for acute GVHD daily during initial hospitalization, at least once weekly after initial discharge during the first 100 days, and at routine follow-up evaluations at the transplant centers at 6 months, 1 year and at least yearly thereafter. Diagnosis of acute GVHD was based on clinical criteria with histopathologic confirmation when possible. Overall staging was based on published criteria and assigned by the medical staff at each institution. Patients with clinical stage $\geq$II disease were treated with methylprednisolone ≥ 48 mg/m^2 intravenously. Although method of staging between the two institutions is similar, there has been no independent review of this data. Chronic GVHD was defined by published criteria and documented by tissue biopsy whenever possible. Non-skin tissue biopsy samples were screened for the presence of UCB-Maternal-donor cells when possible.

Statistical analysis

Data regarding transplant patient characteristics, post-transplant complications and outcomes were prospectively collected at Duke University and University of Minnesota. In order to test the equality of the distribution of patient characteristics across centers, Pearson's Chi square test was employed for categorical factors and the generalized Wilcoxon test for continuous variables. The major statistical end points of this study were the Kaplan-Meier estimates of neutrophil engraftment and survival and cumulative incidences of grade II-IV and grade III-IV acute GVHD, chronic GVHD and relapse (for patients with malignant diseases). Event times for neutrophil engraftment were measured from the date of transplantation to date of neutrophil recovery with censoring for early death (i.e., before day 21) or evidence of persistent malignant disease. Patients who had very slow engraftment (i.e., achieved an ANC $\geq 5 \times 10^8$/L after day 42) or failed to have marrow reconstitution of donor origin were scored as graft failures. Event times for platelet engraftment were measured from the date of transplantation to the date of platelet recovery with censoring only for death before 6 months. Event times for GVHD and relapse were measured from date of transplantation to date of event with censoring of patients at death. Univariate comparisons of the major endpoints were completed with 95% confidence intervals using the log-rank statistic. Event times were analyzed as of April 15, 2000.

For purposes of these analyses, patients with malignancy were categorized as having disease at standard risk or at high risk for relapse after transplantation. Patients were considered to have high risk disease if they had 1) acute leukemia in relapse or beyond second complete remission or with a cytogenetic abnormality (e.g., t[4;11] or t[9;22]), 2) chronic myelogenous leukemia (CML) in accelerated phase or blast crisis, 3) juvenile myelomonocytic leukemia (JMML), 4) stage IV neuroblastoma in relapse, 5) a history of or active invasive fungal disease, and 5) a prior autologous transplant; all other patients were considered to have standard-risk disease. Effect of HLA disparity on probabilities of engraftment and acute GVHD took into account graft rejection

and GVHD vectors, respectively. When both the donor and recipient were heterozygous at the mismatched locus, the disparity was present for both the graft rejection and GVHD vectors. When the donor was heterozygous and the recipient was homozygous or displayed a blank at the mismatched locus, HLA was considered mismatched only in the graft rejection vector and not in the GVHD vector. Conversely, when the recipient was heterozygous and the donor was homozygous at the mismatched locus, the disparity was considered only in the GVHD vector and not the graft rejection vector. Any mismatch, regardless of vector, was considered in the analyses of survival, non-relapse mortality, and relapse.

Results

Neutrophil Recovery (Table 3)

For the 257 patients, the probability of neutrophil recovery by day 42 was 0.87 (0.83-0.92). The median time required to achieve an ANC $\geq 5 \times 10^8$/L was 25 days. In univariate analysis, younger recipient age, lower recipient weight, diagnosis of malignant disease, non-TBI containing preparative regimen, higher UCB unit cell dose, and use of G-CSF were correlated with faster neutrophil recovery and superior engraftment. Notably, HLA disparity had no demonstrable effect on rate of neutrophil recovery or probability of engraftment (p=0.62). Multiple regression analysis is currently being performed.

Interpretation: On the basis of a prior study of this data set a year ago, only higher cell dose and diagnosis of malignant disease were identified as significant factors associated with superior neutrophil recovery and engraftment in multivariate analysis. Recipient age and weight interact with cell dose making it difficult to separate the effects of these variables. A randomized trial would be required to determine if there is any true beneficial effect on the use of G-CSF. Notably, patients undergoing a second transplant using UCB had poorer engraftment; however, reasons for second transplant included graft rejection which may explain this observation. The effect of CD34 dose is currently being explored.

Platelet Recovery (Table 4)

For the 257 patients, the cumulative incidence of platelet recovery by 6 months was 0.51 (0.44-0.58). In univariate analysis, younger recipient age, lower recipient weight, diagnosis of malignant disease, standard risk malignancy, non-TBI containing preparative regimen, CMV negative serostatus, and higher UCB unit cell dose were correlated with faster platelet recovery and superior engraftment. The effect of CD34 cell dose is being explored. Notably, HLA disparity had no demonstrable effect on rate of platelet recovery or probability of engraftment. Multiple regression analysis is currently being performed.

Interpretation: On the basis of a prior study of this data set a year ago, only higher cell dose and CD34 cell dose (not true in this analysis) were significant factors associated with superior platelet recovery and engraftment in multivariate analysis. Recipient age and weight interact with cell dose making it difficult to separate the effects of these variables.

Acute Graft-versus-Host Disease (Table 5)

The overall probabilities of grade II-IV and grade III-IV acute GVHD for the entire group of patients was 0.30 (0.24-0.36) and 0.12 (0.08-0.16) by day 100 after unrelated donor UCB transplantation, respectively. In univariate analysis, no factor was associated with risk of acute GVHD, including degree of HLA disparity. Higher CD3 cell dose was associated with less GVHD; however, this is uninterpretable. Notably, no difference in the probability of grade II-IV

acute GVHD could be discerned between patients treated with CsA plus high dose MP, versus lower dose MP versus other regimens.

Interpretation: On the basis of a prior study of this data set a year ago, no factor was associated with acute GVHD in multivariate analysis. Younger recipient age, HLA match and lower CD3 cell dose are known to be associated with lower GVHD in recipients of unrelated donor marrow but these parameters are not predictive in these analyses.

Chronic Graft-versus-Host Disease (Table 6)

The overall probabilities of chronic GVHD for the entire group of patients was 0.07 (0.04-0.10) at 1 year after unrelated donor UCB transplantation. In univariate analysis, recipient age, recipient weight, use of high dose methylprednisolone and other GVHD prophylaxis, diagnosis of non malignant disease, higher CD3 cell dose, and use of a non-TBI containing regimen were associated with lower risk of chronic GVHD. Also, use of high dose MEL was associate with a higher risk of chronic GVHD.

Interpretation: On the basis of a studies in recipients of unrelated donor marrow, younger recipient age would be expected as a factor associated with less chronic GVHD. Greater HLA disparity and higher CD3 graft content would have been predicted to be associated with more GVHD but this was not observed. Multivariate analyses were not previously performed for this endpoint.

Survival (Table7)

With a median follow up of 1.7 years, the probabilities of survival at 2 year and 4 years after unrelated donor UCB transplantation are 0.45 (0.39-0.52) and 0.41 (0.33-0.48), respectively. The causes of the later deaths were relapse or second malignancy. In univariate analysis, younger recipient age, lower recipient weight, diagnosis of non-malignant disease, standard risk malignancy, recipient CMV negative serostatus, higher graft nucleated cell dose, absence of acute GVHD, use of UCB for primary transplant and caucasian race were associated with improved survival. Increased degree of HLA disparity did not significantly alter the probability of survival after unrelated donor UCB transplantation. Notably, the effect of recipient age and cell dose was preserved even when evaluating those that engrafted. Again, the effect of CD34 cell dose is being explored.

Interpretation: On the basis of a prior study of this data set a year ago, only recipient age and higher cell dose were identified as significant factors associated with superior survival in multivariate analysis. While these results are consistent with the prior analyses, race and history of acute GVHD were not previously assessed. In addition, we evaluated the effect of cell dose specifically in those that achieved engraftment in order to determine whether cell dose had an effect potentially separate from engraftment. The data do suggest that this may be the case. Although degree of HLA disparity does not appear to influence engraftment, GVHD or survival, the pool of patients analyzed predominantly received 1 or 2 HLA antigen mismatched grafts. Therefore a comparison to a population of patients transplanted with fully matched grafts could not be performed.

The causes of death are currently being analyzed. In prior analyses, infection was a predominant cause of death. Immune reconstitution studies are being performed. Again, these data will be made available if requested.

Discussion

In comparison to prior reports on unrelated donor UCB transplantation, the present study benefits from standardized HLA typing with high resolution typing of HLA-DR, greater homogeneity in supportive care treatments, toxicity and GvHD grading, and long-term follow up of transplanted patients at two experienced transplant centers, and the ability to internally verify data accuracy. The principal objective of these analyses was to determine whether specific factors, such as degree of HLA disparity, impacted engraftment, risk of acute or chronic GVHD, non-relapse mortality, relapse and survival. The analysis is ongoing and will be presented on August 14, 2000 and submitted for review for publication in the scientific literature within the next 3 months.

Summary Pertinent Findings

As previously reported, it is notable that graft cell dose (nucleated cell, CD34 cell and/or CFU-GM dose [data not shown]) and not HLA disparity (as defined) are consistently identified as the most important variable for predicting engraftment and survival. These results suggest that vigorous efforts should be made to maximize cell collection and argue for standardization of nucleated cell, progenitor cell and CD34 analyses as additional UCB banks are created and as the possibility of licensing UCB is considered.

In this analysis, there appears to be no adverse effect on engraftment and speed of neutrophil or platelet recovery by increasing HLA disparity as defined and to the level of 2 antigen mismatching. These results contrast with those presented by Gluckman et al and Rubinstein et al who found that HLA identity, in addition to cell dose, was an independent predictor of engraftment. As previously stated, the lack of HLA effect may be related to this data set which contains insufficient numbers of patients receiving 6/6 antigen matched grafts. Furthermore, at the allelic level, the level of mismatching of the majority of these grafts has been grossly underestimated.

An important clinical question is whether HLA-mismatched unrelated donor UCB is less likely to generate severe acute GVHD and extensive chronic GVHD reactions as compared to more closely HLA-matched marrow from adult unrelated donors. Kernan et al reported an incidence of grade III-IV GVHD of 0.47 ± 0.06 for a heterogeneous population transplanted with unrelated donor marrow, including both younger and older recipients and recipients of unmanipulated and T cell depleted marrow. Davies et al. reported an incidence of grade III-IV GVHD of 32-49% depending upon the degree of HLA disparity (0 versus 1). In both instances, the probability of severe acute GVHD was influenced by recipient and donor age and degree of HLA disparity with a lower risk observed in patients $\leq$18 years of age or in patients with HLA matched donors. In a study reported by Balduzzi et al. in a pediatric population, 42-60% of children had grade III-IV acute GVHD depending upon degree of HLA disparity (0 versus 1) and 37% risk of extensive chronic GVHD. As the frequency of grades III-IV acute GVHD in the present study was 12%, these data suggest that unrelated UCB may be associated with a reduced risk of severe acute and extensive chronic GVHD despite greater HLA disparity even when taking into consideration the age of the recipients.

To further assess the value of UCB in comparison to bone marrow from unrelated donors, we formally compared the clinical results using a matched pair analysis. When patients are matched for age, disease and disease status and preparative therapy, the results indicate that HLA 1-2 antigen mismatched UCB should be considered an acceptable alternative to bone marrow. To summarize, survival was superior in recipients of UCB transplantation when compared to HLA

mismatched bone marrow and equivalent when compared to recipients of HLA matched bone marrow. While not presented in detail, these results clearly suggest that UCB will likely remain an important resource for hematopoietic cell transplantation. The complete data analysis will be made available as requested.

At this time, sufficient laboratory and clinical data exist to define the minimal criteria for UCB units to be used for hematopoietic stem cell transplantation. On the basis of a substantial database, we recommend the following product standards; these include, but are not necessarily limited to:

GENERAL PRODUCT REQUIREMENTS:

1. Sterility
2. Negative donor (maternal) screening for HIV, HTLV, Hepatitis B, Hepatitis C, RPR, CMV antigenemia
3. Negative donor (baby or UCB unit) screening for a homozygous hemoglobinopathy (or the presence of two different defective genes affecting the same hemoglobin chain)
4. Availability of precryopreservation viable cell counts and a differential (CD34 counts or CFU-GM are desirable but not essential)
5. Unit storage in liquid nitrogen.
6. Availability of test vials of donor (baby) plasma, DNA and viable cells for additional testing by the transplant center. Availability of test vials of maternal plasma and DNA for additional testing by the transplant center.
7. At least 2 segments must be attached to the unit before cryopreservation.
8. Availability of HLA and ABO/Rh typing
9. Unit shipment to the transplant center in a vessel that maintains a temperature <150 degrees C.

RECIPIENT-SPECIFIC REQUIREMENTS:

1. Unit must deliver a minimum of $\geq 1.5 \times 10^7$/kg recipient body weight.
2. Recipient/donor unit HLA disparity must be ≤ 3 antigens, using serologic level class I A and B typing and high resolution class II DRB1 typing, without restriction as to what antigens are disparate.

Summary

In summary, we have demonstrated that cryopreserved UCB from HLA 0-3 antigen mismatched unrelated donors contains sufficient numbers of transplantable hematopoietic stem and progenitor cells for most patients. Results are at least comparable to those obtained with 1 and 2 antigen mismatched adult unrelated bone marrow. In addition to rapid availability and low rate of Herpes virus contamination of unrelated donor UCB, the data presented indicate that the probabilities of grade III-IV acute GVHD and extensive chronic GVHD are low. Moreover, the results of this statistical analysis demonstrate the importance of graft cell dose in determining outcome after unrelated donor UCB transplantation. Within the group of patients with either an HLA 1 or HLA-2 antigen disparate donor, the data would suggest that graft cell dose rather than degree of HLA disparity has the most significant impact upon the probabilities of engraftment, non-relapse mortality and survival. Therefore, these data suggest that the choice of UCB graft should be based primarily on cell dose rather than degree HLA disparity for patients with more than one HLA 1-2 antigen disparate UCB units. The tolerability of HLA-2 antigen disparate

grafts will likely increase the availability of HSC transplantation, particularly for patients with infrequent HLA haplotypes. The importance of cell dose on transplant outcomes provide the most compelling argument for focusing on the collection of larger UCB grafts and for investigating ex vivo HSC expansion for future clinical trials.

As previously stated, the analysis is ongoing and the results of the multivariate analysis may provide additional information pertinent to the development of product standards. This will be completed over the next several weeks prior to the open meeting on August 14, 2000. These data will be made available to the Food and Drug Administration as requested. If there are additional questions about the data or our interpretation of the data and if additional analyses are desired, please contact us at any time.

Sincerely yours,

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and

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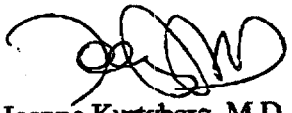

Joanne Kurtzberg, M.D.
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Director, Pediatric Bone Marrow Transplant Program
Duke University Medical Center

Table 1 **Patient demographic and treatment characteristics**

CHARACTERISTIC	NUMBER
Recipient's age (years)	
Median (range)	8.5 (0.2 - 58)
Recipient's weight (kg)	
Median (range)	24.5 (3.9 – 102.8)
Recipient's sex	
Male/Female	152 (59%) /105 (41%)
Recipient's CMV serostatus	
Neg/Pos/Unavailable	142 (55%) / 109 (42%) / 6 (2%)
Recipient's Diagnosis	Total (% of total)
Malignant Disease	164 (64%)
ALL	74 (29%)
AML	56 (22%)
CML	18 (7%)
JMML	5 (2%)
CLL	1 (<1%)
NHL / HD	4 (1%) / 1 (<1%)
Neuroblastoma	5 (2%)
Recipient's Diagnosis	
Non-Malignant Disease	93 (36%)
SAA/FA	19 (7%)
BD/Osteopetrosis	7 (3%)
MDS (RA)	9 (3%)
Immune Deficiency	16 (6%)
Metabolic Disease	42 (16%)
Degree of HLA Match*	
6/6 antigens	18 (7%)
5/6 antigens	90 (35%)
4/6 antigens	123 (48%)
3/6 antigens	15 (6%)
NA**	11 (4%)
Treatment	
TBI/no TBI	168 (65%) / 34 (35%)
G-CSF/no G-CSF	235 (91%) / 22 (9%)
HD MP/LD MP/Other	50 (19%) / 186 (72%)/ 21 (8%)

ALL=acute lymphocytic leukemia; AML=acute myelocytic leukemia; CML=chronic myelogenous leukemia; JMML=juvenile myelomonocytic leukemia; CLL=chronic lymphocytic leukemia; NHL=nonHodgkin lymphoma; SAA=severe aplastic anemia; FA=Fanconi anemia; BD=Blackfan Diamond syndrome; MDS (RA)=myelodysplastic syndrome (refractory anemia); TBI=total body irradiation; no TBI=any conditioning regimen without TBI; G-CSF=prophylactic granulocyte colony stimulating factor; HD MP/LD MP=high dose/low dose methylprednisolone as part of acute GVHD prophylaxis. *Maximal degree of HLA disparity not considering the graft rejection or GVHD vector. **NA=not available due to absence of high resolution DRB1 assignment.

Table 2 **UCB graft characteristics**

CHARACTERISTIC	NUMBER
Nucleated cell dose (pre-cryopreservation) Median (range)	3.7×10^7/kg (0.7 – 57.9)
CD34 cell dose (post-thaw) Median (range)	3.3×10^5/kg (0.2 – 105)
CD3 cell dose (post-thaw) Median (range)	7.0×10^6/kg (0.0 –101)

Table 3. Univariate Analysis for Various Risk Factors on **Neutrophil Engraftment**

Factor	N	# engrafted	Day 45 Engraftment (95% C.I.)[i]	Median	P
Overall	257	212	87% (83 - 92%)	25(10-59)	
median (range)					
# engrafted – 212					
*# engrafted after day 45 – 7 **					
# leuk relapse – 4			** - treated as failures in analysis*		
# died before day 28 w/o engrafting – 12					
*# died after day 28 w/o engrafting – 5 **					
*# defined as graft rejection – 15 **					
*# received 2nd infusions w/o engrafting – 2 **					
Age at Transplant					
0-1	63	56	91% (84 - 99%)	20(10-53)	**<.01**
2-9	91	80	92% (86 - 98%)	26(10-59)	
10-17	53	41	84% (73 - 95%)	26(12-50)	
≥ 18	50	35	77% (65 - 89%)	28(12-47)	
Weight at Transplant					
<10 kg	42	39	95% (88 - 100%)	19(10-53)	**<.01**
11-19 kg	65	55	90% (82 - 97%)	24(10-54)	
20-49 kg	75	62	89% (82 - 97%)	26(13-59)	
≥ 50 kg	75	56	80% (70 - 89%)	27(12-47)	
HLA Disparity (Overall)					
0 antigen mm	18	12	83% (61 - 100%)	30(13-53)	.32
1 antigen mm	91	81	93% (87 - 98%)	23(10-47)	
2 antigen mm	124	98	83% (77 - 90%)	26(12-59)	
3 antigen mm	15	13	91% (75 - 100%)	23(10-34)	
HLA Disparity (Graft Vector)					
0 antigen mm	26	20	90% (76 - 100%)	30(13-53)	.62
1 antigen mm	99	86	92% (86 - 98%)	24(10-47)	
2 antigen mm	113	20	83% (76 - 90%)	26(10-59)	
3 antigen mm	10	8	87% (63 - 100%)	24(10-34)	

Factor	N	# engrafted	Day 45 Engraftment (95% C.I.)	Median	P
Diagnosis					
non-malignancy	93	80	91% (85 - 97%)	22(10-45)	**.04**
malignancy	164	132	85% (80 - 91%)	27(12-59)	
SAA/FA	19	12	70% (48 - 92%)	37(13-43)	**.05**
CML	18	14	87% (69 - 100%)	27(12-37)	
Other	220	186	89% (85 - 93%)	24(10-59)	
Malignancy Risk					
Standard	43	39	93% (85 - 100%)	27(12-59)	.55
High	120	92	82% (75 - 90%)	26(12-54)	
Preparative Regimen					
no TBI	87	75	90% (84 - 97%)	20(10-53)	**<.01**
TBI	168	136	87% (81 - 92%)	27(12-59)	
CMV Serostatus					
Negative	141	119	88% (82 - 93%)	24(10-54)	.32
Positive	110	87	86% (79 - 93%)	26(10-59)	
Prophylactic G-CSF (University of Minnesota only)					
No	22	15	86% (69 - 100%)	31(17-45)	**.02**
Yes	43	40	93% (85 - 100%)	22(10-54)	
Cord Dose					
<1.5 ($x10^7$/kg)	20	15	75% (56 - 94%)	31(13-39)	**<.01**
1.5-2 ($x10^7$/kg)	81	61	86% (77 - 94%)	26(13-47)	
3-5 ($x10^7$/kg)	74	63	90% (83 - 97%)	27(12-59)	
≥6 ($x10^7$/kg)	82	73	90% (84 - 97%)	19(10-53)	
CD34 Dose (University of Minnesota only)					
< 1.5 ($x10^5$/kg)	11	9	82% (59 - 100%)	29(17-54)	**<.01**
1.5-2.2 ($x10^5$/kg)	10	9	90% (71 - 100%)	33(21-45)	
2.2-5 ($x10^5$/kg)	13	13	100%	19(13-38)	
> 5 ($x10^5$/kg)	12	11	92% (76 - 100%)	18(10-31)	

Factor	N	# engrafted	Day 45 Engraftment (95% C.I.)	Median	P
2nd Transplant					
No	238	195	100%	22(14-41)	
Yes	19	17	87% (82 - 91%)	26(10-59)	**.04**

[i] Estimates calculated by Kaplan-Meier estimation

Table 4 Univariate Analysis for Various Risk Factors on **Platelet Engraftment**

Characteristic	N	# engrafted	6 month Incidence(95%C.I.)[i]	Relative Risk(95%C.I.)	P	6 month Mortality (95%C.I.)
Overall	257	131	51% (44-58%)			35% (29-41%)
Median (range)						
# engrafted – 131						
*# engrafted after 6 months – 11 **						
*# alive w/o engrafting – 2 **				** - treated as failures in analysis*		
# died before 6 months w/o engrafting – 89						
*# died after 6 months w/o engrafting – 5 **						
*# defined as graft rejection – 15 **						
*# received 2nd infusions w/o engrafting – 4 **						
Age at Transplant						
0-1	63	47	75%(59-91%)	1.0		21%(11-31%)
2-9	91	43	47%(35-59%)	0.4(.3-.6)	**<.01**	36%(26-46%)
10-17	53	23	43%(28-58%)	0.3(.2-.6)	**<.01**	40%(26-54%)
18+	50	18	36%(21-51%)	0.3(.2-.5)	**<.01**	44%(30-58%)
Weight at Transplant						
< 10 kg	42	30	71%(52-90%)	1.0		24%(11-37%)
10-19 kg	65	37	57%(42-72%)	0.6(.4-1.0)	.06	35%(23-47%)
20-49 kg	75	35	47%(35-59%)	0.4(.3-.7)	**<.01**	33%(22-44%)
50+ kg	75	29	39%(27-51%)	0.3(.2-.5)	**<.01**	41%(29-53%)
HLA Disparity (overall)						
0 ant mm	18	9	50%(24-76%)	1.0		28%(8-48%)
1 ant mm	91	55	60%(48-72%)	1.5(.7-3.0)	.29	26%(17-35%)
2 ant mm	124	58	47%(37-57%)	1.0(.5-2.1)	>.80	40%(31-49%)
3 ant mm	15	6	40%(17-63%)	0.7(.3-2.1)	.56	40%(16-64%)

Characteristic	N	# engrafted	6 month Incidence(95%C.I.)	Relative Risk(95%C.I.)	P	6 month Mortality(95%C.I.)
HLA Disparity (graft vector)						
0 ant mm	26	16	62%(39-85%)	1.0		23%(7-39%)
1 ant mm	99	58	59%(47-71%)	1.0(.5-1.7)	>.80	29%(20-38%)
2 ant mm	113	50	44%(34-54%)	0.6(.4-1.1)	.12	41%(31-51%)
3 ant mm	10	4	40%(5-65%)	0.5(.2-1.4)	.19	30%(4-56%)
Diagnosis						
non-malignancy	93	58	62%(50-74%)	1.0		23%(15-31%)
malignancy	164	73	45%(36-54%)	0.6(.4-.8)	**<.01**	42%(34-50%)
SAA/FA	19	6	32%(11-53%)	0.5(.2-1.2)	.15	37%(15-59%)
CML	18	7	39%(15-63%)	0.7(.3-1.4)	.30	44%(19-67%)
Other	220	118	54%(46-62%)	1.0		34%(28-40%)
Malignancy Risk						
standard	43	13	60%(42-78%)	1.0		31%(17-45%)
high	120	46	38%(28-48%)	0.6(.4-1.0)	**.04**	46%(36-56%)
Preparative Regimen						
no TBI	87	51	59%(46-72%)	1.0		33%(23-43%)
TBI	168	80	48%(39-57%)	0.6(.5-.9)	**.01**	36%(29-43%)
CMV Serostatus						
negative	141	86	61%(51-71%)	1.0		24%(17-31%)
positive	110	40	37%(27-47%)	0.6(.4-.9)	**.01**	49%(39-59%)
Prophylactic G-CSF (University of Minnesota only)						
no	22	12	55%(30-80%)	1.0		27%(9-45%)
yes	43	27	63%(46-80%)	1.1(.6-2.2)	.78	26%(13-39%)
Cord Dose						
<1.5 (x10^7/kg)	20	8	40%(18-62%)	1.0		30%(11-49%)
1.5-2 (x10^7/kg)	81	31	38%(26-50%)	1.2(.6-2.7)	.59	46%(35-57%)
3-5 (x10^7/kg)	74	41	55%(42-68%)	1.6(.7-3.3)	.25	26%(16-36%)
≥6 (x10^7/kg)	82	51	63%(50-76%)	2.7(1.3-5.8)	**<.01**	34%(24-44%)

Characteristic	# N	engrafted	6 month Incidence(95%C.I.)	Relative Risk(95%C.I.)	P	6 month Mortality(95%C.I.)
CD34 Dose (University of Minnesota only)						
<1.5 (x10^5/kg)	11	4	36%(10-52%)	1.0		55%(27-83%)
1.5-2.2 (x10^5/kg)	10	6	60%(29-91%)	1.0(.3-3.5)	>.80	20%(0-41%)
2.2-5 (x10^5/kg)	13	11	85%(57-100%)	1.9(.6-6.0)	.27	8%(0-20%)
>5 (x10^5/kg)	12	8	67%(37-100%)	1.2(.4-4.0)	.76	25%(4-46%)

[i]Cumulative incidences

Table 5 Univariate Analysis for Various Risk Factors on **Acute GvHD**

Factor	N	# w/ GvHD	Grade III-IV Acute GvHD @ Day 100 (95% C.I)			Non-GvHD Mortality
Overall	257	31	12%(8-16%)			28%(23-33%)

Factor	N	# w/ GvHD	Grade II-IV Acute GvHD @ Day 100 (95% C.I.)[i]	Relative Risk (95% CI)	P	Non-GvHD Mortality
Overall	257	77	30%(24-36%)			23%(18-28%)
Age at Transplant						
0-1	63	17	27%(16-38%)	1.0		16%(7-25%)
2-9	91	29	32%(22-42%)	1.2(.7-2.2)	.58	21%(13-29%)
10-17	53	17	33%(20-46%)	1.3(.7-2.5)	.48	19%(9-29%)
≥ 18	50	14	28%(16-40%)	1.1(.6-2.3)	.74	40%(26-54%)
Weight at Transplant						
<10 kg	42	10	24%(11-37%)	1.0		17%(6-28%)
11-19 kg	65	23	36%(24-48%)	1.6(.8-3.4)	.20	24%(13-35%)
20-49 kg	75	22	30%(20-40%)	1.3(.6-2.7)	.55	18%(10-26%)
≥50 kg	75	22	29%(19-39%)	1.3(.6-2.7)	.50	32%(21-43%)
GvHD Prophylaxis						
other	21	6	29%(10-48%)	1.0		43%(21-65%)
low dose MP	186	56	30%(24-36%)	0.9(.4-2.2)	>.80	22%(16-28%)
high dose MP	50	15	30%(17-43%)	0.9(.4-2.3)	>.80	18%(8-28%)
HLA Disparity (GVHD vector)						
0 antigen mm	21	5	24%(6-42%)	1.0		33%(13-53%)
1 antigen mm	98	29	30%(21-39%)	1.2(.5-3.0)	.75	18%(10-26%)
2 antigen mm	115	34	30%(22-38%)	2.0(.5-3.1)	.72	25%(17-33%)
3 antigen mm	14	5	36%(11-61%)	1.5(.4-5.1)	.54	29%(6-52%)
Diagnosis						
non-malignancy	93	26	28%(19-37%)	1.0		16%(9-23%)
malignancy	164	51	31%(24-38%)	1.1(.7-1.7)	.72	27%(20-34%)

Factor	N	# w/ GvHD	Grade II-IV Acute GvHD @ Day 100 (95% C.I.)	Relative Risk (95% CI)	P	Non-GvHD Mortality
Nucleated Cell Dose						
<1.5 (x10^7/kg)	20	9	45%(23-67%)	1.0		25%(6-44%)
1.5-2 (x10^7/kg)	81	21	26%(16-36%)	0.6(.3-1.4)	.23	34%(23-45%)
3-5 (x10^7/kg)	74	26	36%(25-47%)	0.9(.4-1.9)	.72	12%(5-19%)
≥6 (x10^7/kg)	82	21	26%(17-35%)	0.6(.3-1.2)	.15	22%(13-31%)
CD3+ Cell Dose						
<4(x10^6/kg)	54	19	35%(22-48%)	1.0		33%(20-46%)
4-7(x10^6/kg)	57	15	27%(15-39%)	0.6(.3-1.3)	.19	16%(7-25%)
8-14(x10^6/kg)	40	10	26%(12-40%)	0.7(.3-1.4)	.30	24%(10-38%)
≥14(x10^6/kg)	54	11	20%(10-30%)	0.5(.2-1.0)	**.05**	15%(6-24%)
Recipient CMV Serostatus						
negative	141	38	26%(19-33%)	1.0		19%(13-25%)
positive	110	36	32%(23-41%)	1.3(.8-2.1)	.23	30%(21-39%)
Preparative Regimen						
no TBI	87	21	24%(15-33%)	1.0		23%(14-32%)
TBI	168	56	34%(27-41%)	1.5(.9-2.4)	.13	24%(17-31%)
No MEL	129	37	29%(21-37%)	1.0		18%(12-24%)
Low dose MEL	56	16	29%(17-41%)	1.0(.5-1.7)	>.80	30%(18-42%)
High dose MEL	72	24	33%(22-44%)	1.1(.7-1.9)	.65	26%(16-36%)
Prophylactic G-CSF (Universitiy of Minnesota only)						
No	22	8	36%(16-56%)	1.0		32%(13-53%)
Yes	43	16	39%(24-54%)	0.9(.4-2.1)	.79	10%(1-19%)

[i]Cumulative incidence

Table 6 Univariate Analysis for Various Risk Factors on **Chronic GvHD**

Factor	N	N @ 100 days	# w/ GvHD	Chronic GvHD @ 1 year (95% C.I.)	RR (95% CI)	P	Non-GvHD Mortality
Overall	257	166	16	7% (4-10%)			48% (42-54%)
Age at Transplant							
0-1	63	0	48	0%		**<.01**[i]	31% (19-43%)
2-9	91	4	62	5% (1-9%)			48% (37-59%)
10-17	53	8	32	16% (6-26%)			50% (36-64%)
≥ 18	50	4	24	8% (1-15%)			69% (53-85%)
Weight at Transplant							
<10 kg	42	0	32	0%		**<.01**[i]	32% (17-47%)
11-19 kg	65	1	43	2% (0-5%)			47% (34-60%)
20-49 kg	75	6	50	8% (2-14%)			43% (31-55%)
≥ 50 kg	75	9	41	12% (4-20%)			63% (50-76%)
GvHD Prep							
ld methylpred	186	125	16	9% (5-13%)		**.05**[i]	45% (22-68%)
hd methylpred	50	30	0	0%			54% (39-69%)
other	21	11	0	0%			62% (39-85%)
HLA Disparity (gvhd vector)							
0 antigen mm	21	13	2	10% (0-22%)	1.0		48% (26-70%)
1 antigen mm	98	71	3	3% (0-6%)	0.2 (.1-1.5)	.13	41% (31-51%)
2 antigen mm	115	71	8	7% (2-12%)	0.7 (.2-3.4)	.67	53% (43-63%)
3 antigen mm	14	9	1	10% (0-26%)	0.8 (.1-9.3)	>.80	51% (24-68%)
Diagnosis							
non-malignancy	93	71	2	2% (0-5%)	1.0		33% (23-43%)
malignancy	164	95	14	9% (5-14%)	5.9 (1.3-26.1)	**.02**	57% (49-65%)
Cord Dose							
<1.5(x10^7/kg)	20	11	1	5% (0-13%)	1.0		55% (22-88%)
1.5-2(x10^7/kg)	81	43	8	10% (4-16%)	2.1 (.3-16.7)	.49	60% (48-72%)
3-5(x10^7/kg)	74	55	7	10% (3-17%)	1.4 (.2-11.6)	.73	40% (28-52%)
≥6(x10^7/kg)	82	57	0	0%	-		41% (30-52%)

Factor	N	N @ 100 days	# w/ GvHD	Chronic GvHD @ 1 year (95% C.I.)	RR (95% CI)	P	Non-GvHD Mortality
CD3+ Dose							
<4(x10^6/kg)	54	26	7	14% (4-24%)		**<.01**[i]	60% (45-75%)
4-7(x10^6/kg)	57	40	6	11% (3-19%)			44% (30-58%)
8-14(x10^6/kg)	40	26	0	0%			50% (33-67%)
≥14(x10^6/kg)	54	41	0	0%			34% (21-47%)
Recipient CMV Serostatus							
negative	141	102	10	8% (4-12%)	1.0		39% (31-47%)
positive	110	59	6	6% (2-10%)	1.1 (.4-3.1)	>.80	62% (52-72%)
Preparative Regimen							
No TBI	87	58	0	0%		**<.01**[i]	43% (32-54%)
TBI	168	106	16	10% (6-14%)			50% (42-58%)
No MEL	129	94	3	2% (0-4%)	1.0		38% (29-47%)
Low dose MEL	56	31	1	2% (0-5%)	1.1 (.1-10.2)	>.80	61% (46-76%)
High dose MEL	72	41	12	18% (8-28%)	11.2 (3.2-39.8)	**<.01**	57% (44-70%)

[i] P-value from K-M comparison

Table 7. Univariate Analysis for Various Risk Factors on **Survival**

Factor	N	# died	2 Year Survival	4 Year Survival	P
Overall	257	137	45% (39 - 52%)	41% (33-48%)	
Age at Transplant					
0-1	63	21	67% (55 - 79%)	63% (49-77%)	**<.01**
2-17	144	78	43% (35- 52%)	41% (32-50%)	
≥ 18	50	38	23% (10-35%)	11% (0-28%)	
Weight at Transplant					
<10 kg	42	15	64% (49 – 80%)	57% (38-76%)	**<.01**
11-19 kg	65	32	50% (37 – 62%)	50% (37 – 62%)	
20-49 kg	75	38	47% (34 – 60%)	35% (16-54%)	
≥ 50 kg	75	52	29% (18 – 40%)	26% (15-37%)	
Recipient Gender					
Male	152	82	45% (37 – 55%)	42% (33 – 51%)	>.80
Female	105	55	45% (35 – 56%)	39% (27 – 52%)	
HLA Disparity					
0 antigen mm	18	10	41% (17 – 65%)	41% (17 – 65%)	.29
1 antigen mm	91	42	54% (43 – 65%)	43% (28 – 58%)	
2 antigen mm	124	70	42% (32 – 51%)	40% (31 – 50%)	
3 antigen mm	15	9	34% (7 – 62%)	34% (7 – 62%)	
ABO Match					
match	93	52	44% (33 – 54%)	38% (27 – 50%)	.35
mismatch	92	53	40% (29 – 51%)	32% (17 – 46%)	
minor mismatch	72	32	54% (42 – 66%)	54% (42 – 66%)	
Diagnosis					
non-malignancy	93	35	64% (54 – 74%)	51% (34 – 68%)	**<.01**
malignancy	164	102	35% (27 – 43%)	34% (26 – 42%)	
other	220	113	47% (40 –54%)	44% (36 –51%)	.15
CML	18	12	31% (9 – 54%)	—	
FA/SAA	19	12	41% (18 – 64%)	27% (0 –54%)	

Factor	N	# died	2 Year Survival	4 Year Survival	P
Malignancy Risk					
standard	43	20	48% (32 – 65%)	48% (32 – 65%)	**.02**
high	120	81	30% (22 – 39%)	30% (22 – 39%)	
Preparative Regimen					
no TBI	87	38	57%(46 - 67%)	53%(40 - 65%)	.08
TBI	168	97	40%(32 - 48%)	35%(26 - 44%)	
Prophylactic G-CSF					
no	22	14	41% (20 – 61%)	36% (16 – 56%)	.55
yes	235	123	46% (39 – 53%)	41% (32 – 49%)	
Prophylactic G-CSF (University of Minnesota only)					
no	22	14	41% (20 – 61%)	36% (16 – 56%)	.13
yes	43	18	56% (41 – 72%)	—	
CMV Serostatus					
negative	141	60	57% (48 - 66%)	50% (39 - 61%)	**<.01**
positive	110	76	29% (21 - 38%)	27% (18 - 37%)	
Cord Dose					
<1.5 (x10^7/kg)	20	13	19% (0 - 47%)	—	**<.01**
1.5-2 (x10^7/kg)	81	53	34% (24 - 45%)	32% (22 - 43%)	
3-5 (x10^7/kg)	74	36	47% (34 - 60%)	45% (32 - 58%)	
≥ 6 (x10^7/kg)	82	35	59% (48 - 70%)	49% (34 - 64%)	
CD34 (UofM only)					
<1.5 (x10^5/kg)	11	9	14% (0 - 37%)	—	**<.01**
1.5-2.2 (x10^5/kg)	10	4	60% (30 - 90%)	—	
2.2-5 (x10^5/kg)	13	2	85% (65 - 100%)	—	
> 5 (x10^5/kg)	12	4	67% (40 - 93%)	—	
Race (Minority)					
No	198	95	51% (43 - 58%)	47% (38 - 55%)	**<.01**
Yes	59	42	27% (14 - 39%)	23% (10 - 36%)	

Factor	N	# died	2 Year Survival	4 Year Survival	P
2nd Transplant					
No	238	122	47% (41 - 54%)	42% (34 - 50%)	**.01**
Yes	19	15	21% (3 - 39%)	21% (3 - 39%)	
Acute GvHD (Time Dependent)					
No	180	90	48% (41 - 57%)	45% (37 - 55%)	**.04**
Yes	77	47	40% (6 - 30%)	35% (25 - 49%)	
Engrafted Patients Only					
Age					
<2	56	15	74% (62 - 86%)	69% (55 - 83%)	**<.01**
2-9	80	36	51% (39 - 63%)	51% (39 - 63%)	
10-17	41	24	43% (27 - 60%)	35% (18 - 52%)	
≥ 18	35	24	31% (14 - 47%)	15% (0 - 38%)	
Cord Dose					
<1.5 ($x10^7$/kg)	15	8	47% (21 - 72%)	—	**.01**
1.5-2 ($x10^7$/kg)	61	36	41% (28 - 54%)	39% (26 - 51%)	
3-5 ($x10^7$/kg)	63	28	52% (38 - 66%)	49% (35 - 63%)	
≥ 6 ($x10^7$/kg)	73	27	65% (54 - 76%)	54% (38 - 71%)	
CD34 (University of Minnesota only)					
<1.5 ($x10^5$/kg)	10	8	15% (0 - 40%)	—	**<.01**
1.5-2.2 ($x10^5$/kg)	9	3	67% (36 - 97%)	—	
2.2-5 ($x10^5$/kg)	13	2	85% (65 - 100%)	—	
> 5 ($x10^5$/kg)	11	4	64% (40 - 93%)	—	

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